nishing the clinical data, I am indebted to Dr. A. G. Gerster, attending surgeon to the hospital.

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A CRITICAL SUMMARY OF THE LITERATURE ON THE SERUM DIAGNOSIS OF TUBERCULOSIS.

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Demonstration of the presence of tubercle bacilli constitutes practically certain proof of the existence of tuberculosis, but unfortunately tubercle bacilli are often absent from secretions in just the period in which diagnosis is most important, and the disease is frequently so situated that the bacilli do not gain access to secretions that may be examined. Reaction to tuberculin, while almost absolute as an indication of the existence of tuberculosis, is unfortunately a very uncomfortable method for the patient, and one which the majority of the profession still fear to use. While there is no real evidence that such fears are justified, patients are likely to rebel against the discomfort of a reaction to tuberculin, and it is scarcely probable that this method will ever be very freely used outside of hospitals, as tact in the retention of cases will often interfere even when the procedure would be otherwise advantageous Under these circumstances a method that entails no special distress to the patient, and yet may be considered to give reasonably constant and reliable results, is extremely desirable, and such a method was suggested by the successful use of the Widal reaction in the diagnosis of typhoid fever. Serious stumbling-blocks in the use of this method in tuberculosis lie in the fact that the tubercle bacilli in ordinary cultures are not homogeneously distributed throughout the culture medium, and are not motile. Hence, cessation of motility and clumping of the bacilli cannot be demonstrated, and upon these phenomena depends the recognition of the occurrence of a reaction. It has been shown, however, that in some cultures tubercle bacilli exhibit active movement—whether this is merely corpuscular or is a voluntary movement is unknown—and it is likewise recognized that frequent agitation of liquid cultures of tubercle bacilli will result in a fairly homogeneous distribution of the bacilli throughout the culture medium.

Arloing and Courmont have prepared cultures which they state can be used with success in the serum diagnosis of tuberculosis, and the results claimed by them are so encouraging that the method seems to deserve further investigation than has been accorded it, particularly since the work of other investigators has given striking confirmation of the conclusions reached by Arloing and Courmont. The number of men who have interested themselves in the matter is small, however, the reason for this being evident when one learns of the difficulties attendant upon the preparation of proper cultures and to a lesser extent associated with the performance of the test. A much more extended use of the method is therefore necessary before its value can be determined. The difficulties are, nevertheless, not insuperable, and the subject is so important that its worth should be definitely settled.

The several publications of Arloing and Courmont cover in part the same ground and may be considered together. They emphasize the difficulty in obtaining homogeneous cultures even under favorable circumstances. All cultures cannot be made homogeneous. The method to be followed is the use of the classical glycerin peptone bouillon as a medium, inoculating this with a bacillus which has been grown in the laboratory for a long time and has become decidedly attenuated. The one they have used produced only glandular lesions in guinea-pigs, and did not cause death. A most important point in order to secure homogeneity of the culture is daily agitation. Reinoculations should be made about once a month, using always identically the same culture medium and the same amount of mother culture; the latter should always be of the same age. The new generations become more and more unlike the original ones. The medium becomes cloudy, and microscopical examination shows that the bacilli are almost entirely isolated, though to a slight extent collected in small masses. They show marked morphological changes and variations in staining; they will often grow on ordinary gelatin or bouillon without glycerin; they produce a uniform creamy-white veil on glycerin-agar, and in the liquid medium develop motility which ultimately becomes very marked. Were the successive generations not known one could scarcely recognize them as tubercle bacilli. If they are not agitated, however, but left to grow undisturbed they gradually reacquire their ordinary morphological and tinctural characteristics, and form cultures of the usual appearance. Months of patient effort are required to develop a properly homogeneous and motile culture.

When the test is to be carried out one should use a rich culture eight to twelve days old; if the culture is more than two weeks old the reaction is usually unsatisfactory. The technique is more difficult than in carrying out the reaction with typhoid serum. One should take only the upper portion of the culture, as the lower part usually contains small masses of bacilli. The blood from the patient should be drawn into small tubes, and the serum may then be obtained by allowing the clot to retract spontaneously or by centrifugation. The tubes and the finger from which the blood is drawn should be well sterilized before the puncture. Reaction does not occur with normal serum in a dilution of as much as 1 to 5, and in tubercular subjects it rarely occurs in dilutions greater than 1 to 20. Hence, we should mix in small tubes proportions of serum and culture of 1 to 5, 1 to 10, and 1 to 20. After this the tubes should be kept inclined at an angle of about 45°, and examined after two, ten, and twenty-four hours. Subsequent changes have no significance. If reaction occurs one observes with the naked eye more or less complete clarification of the mixture, and a deposit of small flakes along the lower edge of the tube, and microscopically one sees that the bacilli have formed clumps and are no longer motile. The macroscopical examination is facilitated by holding the tube over a black surface; in the microscopical examination it is important to handle the tubes gently, as the clumps are easily broken up.

Dubard seems to be the only one besides Arloing and Courmont who has prepared cultures of his own. The value of the reaction has been investigated by Mongour and Buard and by Bendix, but they obtained their cultures from Arloing and Courmont. Dubard used Ferran's method, and obtained cultures with characteristics closely corresponding to those described by Arloing and Courmont.

The clinical results reported by the originators of the method concern examinations of 186 persons. Of these 128 gave a positive reaction, while 58 were negative; 96 of the positive cases were known to be tuberculous, or proved to be so; 10 of the negative cases were also definitely known to have tuberculosis—a fact which would appear at once to speak strongly against the value of the test were it not that they were all advanced cases, and that in the use of tuberculin it is well known that frequently no reaction occurs in advanced cases, because there is already excessive intoxication with tuberculin; and the animal experiments of Arloing and Courmont, which will be quoted, showed that very virulent or severe infections give no serum reaction. The two methods of diagnosis are therefore alike as to this point, but it does not reduce the value of either as a diagnostic measure, as diagnosis in such cases is practically always easy. If these cases are excluded from the statistics, Arloing and Courmont had 100 per cent. of positive reactions in cases known to be tuberculous. In affections considered to be other than tuberculosis they had 26 positive reactions in 60 cases; 9 of these, who were subsequently examined at autopsy, showed the presence of tuberculosis; it had not been suspected by the clinician in any of the cases. Twenty apparently healthy persons were examined, and six gave the reaction. There was no opportunity for determining whether these six subsequently showed tuberculosis or not. The authors compare these results with those of Beck, whose statistics concerning the diagnostic use of tuberculin are the largest extant, and decide justly, so far as their figures go, that their method gives about the same results as tuberculin, and that each method proves the value of the other.

Mongour and Buard first recorded four cases of pleurisy, nine of pulmonary tuberculosis, and seventeen cases with various affections. Of the cases of pleurisy, three which were certainly tuberculous were positive, the other, which proved to be not tuberculous, was negative. The cases of phthisis were all positive; in one the clinical diagnosis was in doubt, but autopsy showed a tuberculous cavity. The seventeen other cases gave very interesting results. They included instances of rheumatism, epilepsy, hæmoptysis, and various other affections. In all but two the result of the reaction corresponded with the subsequent clinical course or with the conditions found at autopsy, and in some of them the positive reaction led to careful physical examination and the discovery of tuberculosis, which had previously been entirely unsuspected. For example, in a case of chronic rheumatism that had been under observation for six years with no symptoms suggesting tuberculosis, examination after a positive reaction led to the discovery of râles in the apices and of tubercle bacilli in the sputum. The two cases which showed discrepancies between the reaction and the post-mortem findings were not of much importance, as the post-mortems were incomplete. The same authors later record twenty-five further observations with results which were similarly favorable to the test, but which cannot readily be summarized. They state that the microscopical observation of the cessation of motility is more satisfactory than the macroscopical test. They consider the test accurate and easy of practice when proper cultures are once at hand.

Correspondingly favorable results are reported by Bendix—normal persons not giving the reaction in dilutions as low as 1 to 3, and persons with diseases other than tuberculosis not responding, while thirty-four of the thirty-six cases with tuberculosis gave distinct reaction, the negative cases being instances of virulent infection. This experience, therefore, corresponds to that of Arloing and Courmont. Besides these investigations of blood serum, Courmont has carried out the reaction with the fluid from fourteen cases of pleurisy with effusion, eight of ascites, one of effusion in the knee-joint, and one of meningeal exudate. In eighteen cases the effusion was due to tuberculous disease, and in only one instance did the fluid fail to give a reaction. The non-tuberculous cases were all negative.

So far, then, as clinical investigations have been carried, all are strongly in favor of the value of the test, except those of Dubard. This author states that he considers the test of relatively little value, but his report is not clear as to details, and it is impossible to determine definitely his reasons for the statement.

A fact which early impressed itself upon Arloing and Courmont was that there were occasionally rather curious results—that repeatedly persons who had such mild grades of tuberculosis that the disease was scarcely discoverable clinically gave reaction in high dilution, while others who were severely ill reacted only in low dilutions or not at all. Arloing and Courmont investigated the reason for this by choosing animals of different species and different degrees of natural immunity to tuberculosis and inoculating them with bacilli of different degrees of virulence and with material from different tuberculous lesions. They learned that it is possible to produce agglutination in the blood serum in all animals investigated, and that the agglutinating power may be developed by different methods of inoculation and by different forms of cultures. But there are definite variations in the readiness with which the agglutination appears. The agglutinating power varies enormously in the first place in proportion to the virulence of the cultures or material inoculated. Weak cultures, for instance, always produce a marked agglutinating power in the dog, guinea-pig, and rabbit, while virulent cultures produced much less marked agglutinating power or none at all. In the cow and goat reaction was obtained after injecting virulent cultures, but the highest reaction was obtainable with the attenuated cultures. In general, the animals reacted in the following series: the dog best, next the rabbit and the goat, then the cow and the guinea-pig. It was evident that the variations in agglutinating power after inoculations depend chiefly upon the resistance of the species to tuberculosis. The guinea-pig, which is most subject to tuberculosis, is also the animal in which agglutinating action is least readily produced, and in general it shows the lowest power of agglutination. On the contrary, the goat, which is very refractory, shows agglutination even after injection of very virulent cultures. The dog, which is moderately susceptible, does not show agglutination after virulent infection, but shows a very high agglutinative power when suffering from mild tuberculosis. The intensity and frequency of agglutination is, therefore, in inverse relation to the virulence of infection and in direct relation to the resistance of the animal infected. There may be other factors which affect the reaction, as the manner of introduction of the infective material, the primary locations of the lesions, associated infections, and the like. There is also to be noted an interesting variation in the rapidity with which the agglutinating power appears. The latter may prove to be of importance in drawing conclusions from the serum diagnosis.

These results indicate that one may expect, in human subjects, that poorly marked reactions or none at all will be seen in those who are suffering from a very severe or virulent infection, and perhaps in those who are excessively susceptible. Experimental work on animals, therefore, gives results entirely similar to those obtained by Arloing and Courmont in working on human subjects, and the same inverse relation between the intensity of infection and the strength of the reaction has been observed by all other workers. It is suggested by Arloing and Courmont that in human subjects as well as in animals it may be demonstrated that agglutination takes place more readily when the bacilli used in the test are homologous to those causing the infection—a very interesting idea and one that may prove very important if the test ever comes to be of decided clinical value.

A review of all this work leads one to conclude that whatever the clinical value of the method may prove to be it deserves to be tested more widely. Undoubtedly the preparation for the work requires a great deal of care and patience, and disheartening failures are likely to be met with in accustoming one's self to the work, particularly in the preparation of proper cultures. This is seen in the fact that all those who have investigated the method, excepting Dubard, have used the culture originally prepared by Arloing and Courmont, and we are led to suspect that others have made ineffectual attempts to prepare satisfactory cultures. But the method would be of enormous value if its general use could be secured and if results proved satisfactory. It requires a laboratory and a skilled bacteriologist; but in this country probably this would not lessen its value to any great extent, even to general practitioners without hospital connections, as our health board laboratories could do the work for them. The aid that it would give the profession in general, if it proved a reliable method, is evident, and the importance of the question would seem to demand efforts to determine its value definitely and to put it at the service of the clinician.

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